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A guide to interpreting economic studies in infectious diseases

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Abstract

Healthcare providers continue to seek improved methods for preventing, detecting and treating diseases that affect human survival and quality of life. At the same time, there will always be financial constraints because of limited societal resources. Many of the discussions on how to provide economically sound solutions to this challenge have not fully engaged the input of clinicians in the field. The purpose of this review is to increase economic knowledge for clinicians. We cover healthcare cost elements and methods used to assign value to a health outcome. We outline the challenges in conducting economic studies in the field of infectious diseases. Finally, we discuss the meaning of efficiency from multiple perspectives, and how the concept of economic externalities applies to infectious diseases.

Keywords: Cost analysis, economic externalities, economics, efficiency, healthcare value, infectious diseases, review

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Introduction

The purpose of economic knowledge for clinicians is to enable them to better understand the forces affecting their workplace, to accurately interpret economic results, and to develop meaningful future research. Cost is an element of any decision [1,2]. Clinicians who understand economics may contribute more effectively to patient, workplace and national decision-making processes. A decision in healthcare may involve choosing between alternative treatment strategies by evaluating cost, quality, and how much is available to spend. Implementing or expanding a service is also an economic decision. Examples in healthcare include aggressive human immunodeficiency virus (HIV) screening, enhanced tuberculosis detection, methicillin-resistant *Staphylococcus aureus* search and destroy methods, improved infection control, and promotion of judicious antimicrobial use [3–11]. We will review healthcare costs and benefits, and how they are measured, and use examples from infectious diseases. The major players in healthcare economics are providers supplying healthcare services, patients receiving the benefits of healthcare, and often third parties, who pay all or most of the bill for services provided [12,13].

Healthcare Costs

On one side of a healthcare transaction is the provider—this may be a clinician, clinic, pharmacy, imaging centre, hospital, or healthcare system. Defining provider cost is difficult in healthcare, because a multitude of goods are produced by a bevy of personnel [14]. They are consumed in seemingly infinite combinations by individual patients. There are also uncertainties in patient diagnosis, severity of illness, testing accuracy, and treatment response, making future cost predictions difficult [12,15]. Cost definitions that are useful in economics are 'fixed', 'variable', and 'marginal' [2,12,13,16–18]. They exist for the patient, hospital and societal perspectives, but are uniquely complex at the hospital level [17].

Hospitals incur costs for building space, equipment, and renovations. Those costs are considered to be fixed from the hospital perspective, because they will not change, despite output or number of patients treated [2,12,13,18]. For example, the cost of buying and installing a computed tomography (CT) scanner is constant, no matter how many scans are performed. The more scans performed, the lower the fixed equipment cost per scan. On the other hand, variable costs do change with output or number of patients treated

[2,12,13,18]. Examples include doses of antibiotics, blood culture bottles, or wound dressings. The more is provided, the higher the cost. Marginal cost is defined as the change in total cost needed to produce one additional unit of output [12,13,19]. It is important to keep in mind that costs depend on the time frame. Although the overall CT cost is high, one more scan only increases the variable cost over the short term. Therefore, marginal costs initially decrease, owing to economies of scale [12,18]. In the CT example, the machine is already paid for, the labour costs per scan are lower, owing to reduced staff idle time, and high-volume purchases of contrast media will lower variable costs. Marginal cost will later rise with continued increases in volume as the facility becomes overwhelmed and inefficient [14]. Semi-fixed costs (also known as step-fixed costs) are non-proportional incremental cost jumps [12]. For example, the fixed cost per CT scan initially drops as the number of scans goes up, until a new scanner and additional technicians are needed to meet demand. Semi-variable costs (also known as mixed costs) have both fixed and variable elements [12]. Examples include utilities and service contracts, which are similar to mobile phone contracts. There is a reliable base or fixed cost unless the number of minutes is exceeded, and then each additional minute costs more. Sunk costs are those that are unaffected by a current decision, or are gone forever [18].

The authors and colleagues have conducted a number of economic studies from the provider economic perspective [13,20–23]. Important study tasks are to identify patient resources used, and then to determine the total cost for each of those resources. For hospital stays, there is the total length of stay, the location of treatment in intensive–care or regular wards, and what tests, treatments and procedures the patient received [20]. One can simply multiply the length of stay by the average cost per day [21]. However, for many cost comparisons, the difference between subgroups will require direct measurement of healthcare resource elements that differ significantly between individual patients. This requires a method for allocating the entire hospital or clinic cost to specific measurable patient services. For example, a CT scan requires an imaging area, the scanner, a technician, a radiologist, and contrast material. Those costs are specific to CT scans, and are designated as 'service' costs [13]. Service costs are directly measureable for individual patients who receive a CT scan. However, there are also costs for the payroll department in managing employee paychecks, and the environmental department in keeping the entire hospital clean, and electrical power expenses to keep the imaging rooms heated and lit, and the scanner operating. These are called 'support' costs, as opposed to service costs [13]. Support costs such as electricity and environmental workers are allocated to each department by the proportion of square footage occupied [13]. Support costs such as worker benefits or payroll departments are allocated by proportion of full-time equivalent employees working [13]. This becomes more complex for large organizations where the environmental department cleans the CT scanner area, the patient-care rooms, the radiologist reading room, and the payroll department offices. The payroll department manages salaries for CT technicians, nurses, and environmental workers.

Errors in allocation can occur unless the interactions between non-patient-care departments, such as environmental and payroll, are accounted for. The multiple-distribution

TABLE 1. Healthcare cost elements and examples

One-time costs
Hospital building—allocated once directly per year
Costs amortized over life of building, resulting in an annual fixed cost
Cost is allocated by square footage occupied by each department
Rent may be a substitute
Capital and equipment—allocated once directly per year; may need replacement or repair
Costs amortized over expected life of equipment
Used in specific departmental areas
Service examples—computed tomography scanners, ventilators
Support examples—administrative office equipment
Annual support costs
Non-salary support—allocated once directly per year
Used throughout the facility
Examples
Cleaning supplies allocated by square footage
Employee benefits allocated by full-time equivalent employees
Salary support—labour costs allocated using multiple distribution
Function throughout the facility
Examples
Environmental allocated by square footage
Payroll allocated by full-time employee equivalents
See Fig. 1 for illustration of allocation of support costs to service centre departments
Service centre costs—labour
Providers: directly provide patient care in hospitals or clinics—physicians, nurses
Tests and treatments—often occupy designated space and use specialized equipment
Pharmacy—pharmacists
Laboratory—technicians, pathologists
Radiology—technicians, radiologists
Procedures: endoscopy, bronchoscopy—specialists
Operating room staff—anaesthesiology, surgeons
Ancillary—work directly in providing patient services to augment or facilitate services
Clinical administration
Clerical staff
Social services
Language interpreter services
Health education
Dietary—provide patient food, dietary consultation, and sometimes staff meals
Indirect patient services—usually added to measured provider visits or ancillary costs
Additional patient costs for an encounter, hospital day, test or treatment
Examples
Medical records
Billing and finance
Hospital information services
Materiel management (procurement, storage and delivery of supplies)
Security
Biohazardous waste disposal
Communications—pagers, phones, maintain contact numbers
Variable service centre costs—consumable supplies
Directly consumed during the provision of healthcare services
Medical supplies—central lines, wound dressings, facemasks
Laboratory supplies—culture bottles, laboratory reagents
Radiological supplies—contrast media
Pharmacy supplies—medicines, vaccines, medication bottles and caps
Miscellaneous—paper, food, patient ID bracelets

method with reiterative equations has been used by the authors [12,13,20–23]. The support department costs are allocated to all service and support departments on the basis of square footage or full-time equivalent employees per department. This results in a proportion of the support cost allocation going back to support departments. This is re-allocated again to all departments, with increasingly more support costs being sequentially added to the patient service departments. In the final step, the total support cost is allocated to service centres only. The final result is that all hospital operating costs are allocated to patient service centres on the basis of estimated use. The cost elements and steps of this allocation process are shown in Table 1 and Fig. 1. All of these costs are considered to be healthcare or hospital perspective costs.

Healthcare efficiency is an important concept. 'Technical efficiency' defines how efficiently patients and healthcare outputs are produced by a facility with its available resources [13,24]. This may require internal re-allocation of resources when conditions change. For example, during the recent H1N1 influenza outbreak, our hospital re-allocated the Observation Unit space and staff to care for H1N1 patients, and anticipated delaying elective surgery to divert respiratory therapists and recovery room nurses to influenza care. In contrast, the goal of 'economic efficiency' for the same healthcare facility is to maximize third-party reimbursements relative to hospital expenditures for healthcare services provided [13,24] (Fig. 2).

Healthcare Benefits or Value

Costs for healthcare ideally lead to benefits or gains in value for patients and society. Healthcare outcomes are difficult to measure. Outcomes may simply be counted: total number of patients treated, lives saved, or years of life saved. We often use surrogate outcomes, such as CD4 counts in AIDS, that have been correlated with health improvements and expected years of life [25,26]. Utility is a concept that can be applied to healthcare outcome measurement [26,27]. Healthcare utility combines quantity of life in years with a health-related value or quality for each year [16,28]. The patient or societal goal is to maximize total utility over time. Individual utility involves consuming a sought-after good in an ideal quantity. For example, how many litres of expired plain vanilla ice cream would you trade for one of your favourite flavour of fresh gelato? The utility of fresh gelato can be measured in how much money you would pay, or in how many litres of plain vanilla ice cream you would trade [29]. Marginal utility is the additional benefit gained from consuming one more quantity of value. The concept of diminishing marginal utility suggests that the first delicious bite of your favourite gelato has more utility than that last bite after eating an entire litre. These concepts are simple when rating the utility of food, but become complex for health status.

In healthcare, we seek to maximize the total number of lives saved, the years of life, and the quality of those years. Many cost-effectiveness and cost–utility studies examine the cost per quality-adjusted life-years (QALYs) saved [26,30,31]. Quality of life refers to general wellbeing. The QALY is on a scale from 1.0, which is perfect health, to 0.0, which is death [29,32]. By using QALYS, one can evaluate alternative healthcare outcomes without requiring any loss of life or years of life [26,32]. All of these ideas have been useful in the study of HIV testing and management. Cost studies have reported the improvements in QALYs gained by treatment of HIV

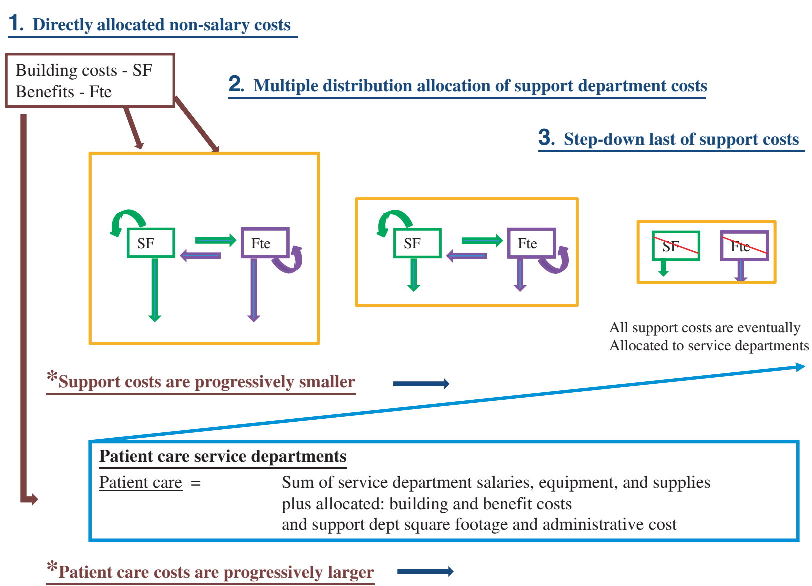

FIG. 1. Multiple-distribution allocation of support cost to service departments to calculate full cost of patient care. Fte, full-time equivalent employee; SF, square-footage.

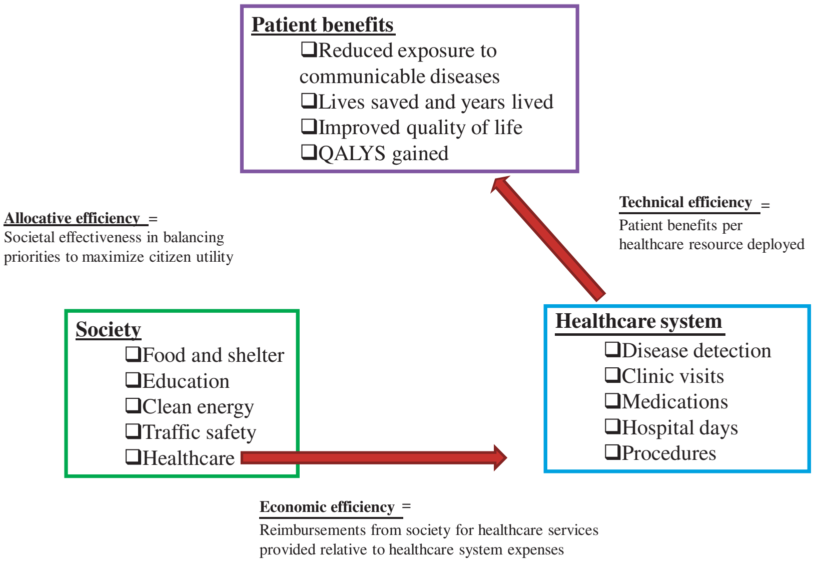

FIG. 2. Efficiency—allocative, technical, and economic. QALY, quality-adjusted life-year.

complications [33,34]. In fact, it has been estimated that highly active antiretroviral therapy (HAART) has resulted in gains of more than 3 million human years of life [35]. More recently, initiating HAART earlier in the course of illness has been recommended [36]. Although the medication will cost more in the short term, this cost is balanced by the benefits of improved health and reduced infectivity. In addition, many have moved from extensive counselling prior to HIV testing to 'opt-out' programmes where HIV testing is routine [37]. The economic benefits of aggressive HIV testing programmes result from early diagnosis and treatment plus reduced HIV transmission [3,37]. This information can be used to estimate the future medical cost savings from prevented HIV infection. Simple observation is another economic study method. For example, the authors and other researchers have reported the cost for treatment of patients with HIV/AIDS for 1 year [20]. These data can be used to estimate savings from prevented HIV infection and early HAART. We found that patients who received comprehensive ambulatory care and maintained high CD4 counts had fewer hospitalizations and lower total annual costs.

Measuring QALYs requires assessing the value of a health state as compared with a better or worse state, and how long that difference continues [26,29,38]. A current health state can be compared to better or worse health states. For example, if an average healthy year has a utility of 0.92, but an untreated spinal epidural abscess causes hemiparalysis, which has a utility of 0.44, then a healthy patient with new hemiparalysis has lost (0.92–0.44) or 0.48 units per year [31,39]. If this disease had been prevented with early diagnosis and treatment, the patient would have gained 4.8 QALYS over 10 years by avoiding hemiparalysis. Economic evaluations of health programmes can be expressed as money spent per QALY gained [26,31,32,38]. QALYs are used to aid society in evaluating resource allocation for diverse outcomes that affect different populations, such as weighing the benefits of improved childhood vaccination rates as compared with deciding what CD4 count warrants starting antiretroviral therapy in HIV patients [32,36].

There are three widely used methods of measuring where different health states rank on this scale: the visual analogue scale, time trade-off, and standard gamble [16,26,29,32,40]. Each method seeks to measure and compare patient or societal preferences for different health states [32,40]. For the visual analogue scale, respondents rate a state of health on a simple linear scale. In time trade-off, respondents choose between remaining in a state of bad health or achieving an improved or perfect state of health, but having a shorter lifespan. In a standard gamble, respondents select one of two choices: remain in a current state of bad health, or undergo a medical intervention with a particular probability of cure and another probability of death. Alternatively, patients can decide what chance of health deterioration they would risk to extend their lifespan. The goal of all these methods is to compare different healthcare strategies and outcomes for a single disorder and across multiple disorders [32].

There are ongoing efforts to better understand and measure health preferences [26,41–43]. When these healthcare assessments are being made, uncertainty and risk must be taken into account [29,42–44]. The risk of treatment and the promise of improved or extended life-expectancy are only probabilities. This often makes it difficult for respondents to accurately complete surveys. Controversy exists on the relative meaning and validity of different health-related quality-of-life survey tools in different settings. One major question is whether the utility scale from 0.0 to 1.0 is linear or equal along its entire span. For example, is it correct to assume that improved health from 0.2 to 0.4 has the same value as that from 0.6 to 0.8? [29] There are also individual disposition effects [41,43]. Some optimistic individuals will continue to rate their current health as high quality, even as they grow older and more frail, whereas young patients with depression rate their quality of life as very low. Health preference results, even in the same domain, can vary with which individuals are questioned and where they are on the scale [44]. Imagine a scale for ambulation or getting from place to place. At one end is a completely dependent bedridden person, and at the other is a fully ambulatory athlete. Bedridden individuals may greatly value being in a wheelchair relative to their current state, whereas athletes may believe that money would be wisely spent in keeping ambulatory people out of wheelchairs, and may imagine being bedridden as worse than death. In other words, quality of life may look better on the way up the scale than on the way down. This phenomenon has even been described for individual patients [43]. Patients with colostomies rate their current health state higher than unaffected patients would rate having an imagined colostomy. However, after treatment, post-colostomy patients also rate the past health status of colostomy lower than those with current colostomies.

From the perspective of society, the goal is to maximize total social utility. When resources are limited, it is difficult to determine which perspective to use in comparing health programmes—the afflicted or non-afflicted? [32,41] Potential health benefits must also be compared with other social goods that may be sacrificed, such as abundant clean energy, effective education, and traffic safety. This is the definition of opportunity cost for society [32]. An opportunity cost represents an alternative good that must be given up, and that would have been the next best use of a resource [16,45]. This leads to the concept of 'allocative efficiency' [42,46]. Allocative efficiency represents the effectiveness of a society in allocating resources to maximize the utility for an entire community over all of its activities and goals (Fig. 2).

Challenges in Study Design and Economic Analysis

Infection prevention programmes are difficult to assess economically. Healthcare-acquired infection (HAI) is an important example. The economic question is whether the investment in HAI prevention will be rewarded with future savings, when infection has been averted [47]. The cost analysis attempts to determine what patients would have cost had they not developed an infection. The first problem in measuring the cost for infection is confounding. The management of more severely ill patients usually requires more testing and treatment procedures, more frequent encounters with healthcare personnel, and prolonged length of stay. The research goal is to determine how much of the expense of hospitalization was attributable to the initial severity of illness and how much was attributable to subsequent development of HAI. The same is true for antimicrobial-resistant infections (ARIs), which are often hospital-acquired or associated with past healthcare encounters and treatments [5,21].

Several methods have been developed to answer this question. Matched case–control methods compare the cost for patients with a specific infection with that of controls who are similar in every other respect, except that they did not develop infection. This usually requires limiting the study to patients who have infection and can be matched to satisfactory controls. For example, in our recent ARI study, only 138 (73%) of a total 188 identified ARI patients could be matched to a suitable control by propensity score. Another strategy is to include all patients, but to use statistical methods, such as ordinary least-squares (OLS) linear regression models, to adjust for patient factors that increase cost [21,48]. Linear regression measures the effect of each cost predictor used in the economic model. It is therefore important to measure other important cost predictors, such as patient severity of illness, comorbidities, and treatment, in high-cost settings such as the intensive-care unit (ICU). Regression parameter estimates represent the cost associated with each predictor, including HAI or ARI. The benefit is that an entire facility might be able to assess its total attributable cost for infection by including all patient subgroups in the analysis. For example, the authors and colleagues used a random sample strategy to estimate the hospital cost for HAI over 1 year [21,22]. Our rationale was that infection control is most effective if it is widely adopted, because patients often transfer between treatment areas such as ICUs or operating rooms to regular wards or recovery rooms.

The potential problem with OLS linear regression analysis is that the method may not be perfectly applicable to healthcare cost data [49–51]. The most familiar distribution in descriptive statistics is the normal bell-shaped curve. In contrast, healthcare cost data tend to be greatly skewed to the right, with just a few patients incurring costs that are much higher than those for the majority [49–51]. If just a few extra HAI or ARI cases are very costly, this could bias the results. One solution is to exclude the very high-cost outliers. The problem is that high-cost outliers do contribute significantly to healthcare cost, and it is probable that patients with HAI and ARI are preventable outliers. There are a number of strategies for addressing the problem of skewed data. Winsorizing can decrease the effect of outliers in skewed datasets while still maintaining them in the analysis [52]. After the dataset is arranged from least to most expensive, the individual cost for each of the extreme outliers can be replaced with the cost of the next patient in the sequence. Analysis can then be conducted on the Winsorized dataset. In describing skewed data, the median is often substituted for the mean as a more accurate representation of the data. In similar fashion, there are statistical methods for dampening the effects of outliers, such as median quantile regression [53]. Another method with which to reduce the effect of outliers is to convert the raw total cost numbers to a logarithm [49–51]. A simple example is using base 10 log, where: 0 = 0; 10 = 1; 100 = 2; 1000 = 3; and so on. This procedure reduces the relative contributions of very high numbers in a dataset that is highly skewed to the right. Generalized linear models use the same concept, and the results can be retransformed back to cost units [54]. Finally, costs can be calculated by multiplying the cost per day by the attributable excess length of stay. However, the longer a patient is in the hospital, the higher the chance of acquiring an infection. This is called endogeneity bias, where linear regression may overestimate the length of stay attributable to infection alone. One method of addressing endogeneity bias is to use a multistate proportional hazard model, which controls for pre-infection length of stay [55]. Our group recently reported cost outcomes for ARI, including comparisons of different analytical methods [21]. For ARI, total hospital costs ranged from $25 641 to $29 069 per patient, depending on the study design and analytical method used. The lowest cost estimate was obtained with OLS linear regression, with adjustments made for surgery, ICU care, comorbidities, and acute severity of illness on admission to the hospital. The highest cost estimate was obtained with a matched case–control design. On further adjustment for concurrent HAI, the cost range was $18 585 to $21 208. Greater cost differences were seen when the same economic analysis was used in different patient settings. The attributable cost for ARI in non-ICU patients was $7200, as compared with $47 727 in ICU patients.

The last important concept in healthcare economics is ‘externalities’ [18,27,45]. The usual economic discussion is focused on the consumer’s payment for a good and the seller’s profit from selling that good. Externalities are the unmeasured effects on third parties who were not at all involved in the primary economic transaction between buyer and seller. A typical example of a societal negative externality is poor air quality caused by pollution from a factory. A positive externality would be the benefit that members of a large apartment complex receive because one of their neighbours has bought and installed very sensitive smoke and carbon monoxide detectors. In the event of a fire, the entire building may benefit from the early alarm. These ideas are also applicable to healthcare, especially infectious diseases. A positive externality in healthcare might result from aggressive HIV and tuberculosis diagnostic testing programmes [11,37]. Ten years from now, citizens may stroll past a hospital and not know that they would have had HIV infections if the hospital had not instituted aggressive HIV testing and treatment programmes 10 years earlier. A negative externality would be the practice of aggressive treatment of mild or suspected infections with broad-spectrum antibiotics [9,28]. The treated patients receive only minimal benefit. Ten years from now, a patient may die of infection caused by an antimicrobial-resistant organism. In fact, recent reports have documented that many who died during the recent H1N1 pandemic had post-influenza pneumonia caused by methicillin-resistant *S. aureus* [56]. The management of infectious diseases may represent a unique example of positive and negative externalities occurring within a single medical practice domain. The decisions made by clinicians today may have effects that will be difficult to quantify economically in the future.

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Transparency Declaration

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References

1. Feldstein PJ. *Health care economics*, 4th edn. Albany, NY: Delmar Publishers, 1993.
2. Suver JD, Neumann BR, Boles KE. *Management accounting for healthcare organizations*, 4th edn. Chicago, IL: Precept Press, 1992.
3. Paltiel AD, Weinstein MC, Kimmel AD *et al.* Expanded screening for HIV in the United States—and analysis of cost-effectiveness. *N Engl J Med* 2005; 352: 586–595.
4. Klevens RM, Edwards JR, Richards CL Jr *et al.* Estimating health care-associated infections and deaths in US hospitals, 2002. *Public Health Rep* 2007; 122: 160–166.
5. Howard D, Cordell R, McGowan JE Jr, Packard RM, Scott RD, Solomon SL. Measuring the economic costs of antimicrobial resistance

in hospital settings: Summary of the Centers for Disease Control and Prevention Emory Workshop. *Clin Infect Dis* 2001; 33: 1573–1578.
6. Goldmann DA, Weinstein RA, Wenzel RP *et al.* Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals: a challenge to hospital leadership. *JAMA* 1996; 275: 234–240.
7. Dellit TH, Owens RC, McGowan JE Jr *et al.* Infectious Diseases Society of America and Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007; 44: 159–177.
8. Cummings KL, Anderson DJ, Kaye KS. Hand hygiene noncompliance and the cost of hospital-acquired methicillin-resistant *Staphylococcus aureus* infection. *Infect Control Hosp Epidemiol* 2010; 31: 357–364.
9. Avorn JL, Barrett JF, Davey PG, McEwen SA, O'Brien TF, Levy SB. *Antibiotic resistance: synthesis of recommendations by expert policy groups. Alliance for the prudent use of antibiotics*. Geneva: World Health Organization, 2001; 1–155.
10. Robicsek A, Beaumont JL, Paule SM *et al.* Universal surveillance for methicillin-resistant *Staphylococcus aureus* in 3 affiliated hospitals. *Ann Intern Med* 2008; 148: 409–418.
11. Miller TL, McNabb SJN, Hilsenrath P *et al.* The societal cost of tuberculosis: Tarrant County, Texas, 2002. *Ann Epidemiol* 2010; 20: 1–7.
12. Finkler SA. *Essentials of cost accounting for health care organizations*. Gaithersburg, MD: Aspen Publishers, 1994.
13. Roberts RR, Frutos PW, Ciavarella GG *et al.* Distribution of variable vs fixed costs of hospital care. *JAMA* 1999; 281: 644–649.
14. Lave JR, Lave LB. Hospital cost functions. *Annu Rev Public Health* 1984; 5: 193–213.
15. Fuchs VR. How to think about future health care spending. *N Engl J Med* 2010; 362: 965–967.
16. Haddix AC, Teutsch SM, Corso PS. *Prevention effectiveness: a guide to decision analysis and economic evaluation*, 2nd edn. New York: Oxford University Press, 2003.
17. Luce BR, Elixhauser A. Estimating costs in the economic evaluation of medical technologies. *Int J Technol Assess Health Care* 1990; 6: 57–75.
18. Samuelson PA, Nordhaus WD. *Economics*, 12th edn. New York: McGraw-Hill Book Company, 1985.
19. Williams RM. The costs of visits to emergency departments. *N Engl J Med* 1996; 334: 642–646.
20. Roberts RR, Kampe LM, Hammerman M *et al.* The cost of care for patients with HIV from the provider economic perspective. *AIDS Patient Care STDS* 2006; 20: 876–888.
21. Roberts RR, Hota B, Ahmad I *et al.* Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. *Clin Infect Dis* 2009; 49: 1175–1184.
22. Roberts RR, Scott RD II, Cordell R *et al.* The use of economic modeling to determine the hospital costs associated with nosocomial infections. *Clin Infect Dis* 2003; 36: 1424–1432.
23. Roberts RR, Zalenski RJ, Mensah EK *et al.* Costs of an emergency department-based accelerated diagnostic protocol vs. hospitalization in patients with chest pain: a randomized controlled trial. *JAMA* 1997; 278: 1670–1676.
24. Valdmanis VG. Ownership and technical efficiency of hospitals. *Med Care* 1990; 28: 552–561.
25. Hogg RS, Yip B, Chan KJ *et al.* Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA* 2001; 286: 2568–2577.
26. Neumann PJ, Zinner DE, Wright JC. Are methods for estimating QALY's in cost-effectiveness analyses improving? *Med Decis Making* 1997; 17: 402–408.
27. Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-effectiveness in health and medicine*. New York: Oxford University Press, 1996.
28. Meropol SB. Valuing reduced antibiotic use for pediatric acute otitis media. *Pediatrics* 2008; 121: 669–673.
29. Torrance GW. Utility measurement in healthcare: the things I never got to. *Pharmacoeconomics* 2006; 24: 1069–1078.
30. Rasanen P, Roine E, Sintonen H, Semberg-Kontinnen V, Ryynanen OP, Roine R. Use of quality-adjusted life years for estimation of effectiveness of health care: a systematic literature review. *Int J Technol Assess Health Care* 2006; 22: 235–241.
31. NHS. Measuring effectiveness and cost effectiveness: the QALY. 2010. Available at: http://www.nice.org.uk/newsroom/features/measuringeffectivenessandcosteffectivenesstheqaly.jsp (last accessed 16 September 2010).
32. Weinstein MC, Torrance G, McGuire A. QALY's: the basics. *Value Health* 2009; 12: S5–S9.
33. Freedberg KA, Losina E, Weinstein MC *et al.* The cost effectiveness of combination antiretroviral therapy for HIV disease. *N Engl J Med* 2001; 344: 824–831.
34. Severe P, Juste MAJ, Ambroise A *et al.* Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med* 2010; 363: 257–265.
35. Walensky RP, Paltiel AD, Losina E *et al.* The survival benefits of AIDS treatment in the United States. *J Infect Dis* 2006; 194: 11–19.
36. Thompson MA, Aberg JA, Cahn P *et al.* Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society—USA panel. *JAMA* 2010; 304: 321–333.
37. Haukoos JS, Hopkins E, Conroy AA *et al.* Routine opt-out rapid HIV screening and detection of HIV infection in emergency department patients. *JAMA* 2010; 304: 284–292.
38. Rick S, Loewenstein G. Intangibility in intertemporal choice. *Phil Trans R Soc Lond B Biol Sci* 2008; 363: 3813–3824.
39. Gold MR, Franks P, McCoy KI, Fryback DG. Toward consistency in cost-utility analyses: using national measures to create condition-specific values. *Med Care* 1998; 36: 778–792.
40. Arnesen T, Trommald M. Are QALY's based on time trade-off comparable? A systematic review of TTO methodologies. *Health Econ* 2005; 14: 39–53.
41. Dolan P. Developing methods that really do value the 'Q' in the QALY. *Health Econ Policy Law* 2008; 3: 69–77.
42. Garrison LP. Editorial: on the benefits of modeling using QALY's for societal resource allocation: the model is the message. *Value Health* 2009; 12: S36–S37.
43. Smith DM, Brown SL, Ubel PA. Are subjective well-being measures any better than decision utility measures? *Health Econ Policy Law* 2008; 3: 85–91.
44. Kahneman D, Tversky A. Prospect theory: an analysis of decision under risk. *Econometrica* 1979; 47: 263–292.
45. Palmer S, Raftery J. Economic notes: opportunity cost. *BMJ* 1999; 318: 1551–1552.
46. Donaldson C, Currie G, Mitton C. Cost-effectiveness analysis in health care: contraindications. *BMJ* 2002; 325: 891–894.
47. Perencevich EN, Stone PW, Wright SB *et al.* Raising standards while watching the bottom line: making a business case for infection control. *Infect Control Hosp Epidemiol* 2007; 28: 1121–1133.
48. Kleinbaum DG, Kupper LL, Nizam A, Muller KE. *Applied regression analysis and other multivariable methods*, 4th edn. Belmont: Duxbury Press, 2008.
49. Manning WG. The logged dependent variable, heteroscedasticity, and the retransformation problem. *J Health Econ* 1998; 17: 283–295.
50. Manning WG, Mullahy J. Estimating log models: to transform or not to transform? *J Health Econ* 2001; 20: 461–494.

51. Mullahy J. Econometric modeling of health care costs and expenditures: a survey of analytical issues and related policy considerations. *Med Care* 2009; 47: 104–108.
52. Buckley JA, Georgianna TD. Analysis of statistical outliers with application to whole effluent toxicity testing. *Water Environ Res* 2001; 73: 575–583.
53. Chen CL. An introduction to quantile regression and the QUANTREG procedure. Paper 213-30. SAS Institute Inc. Available at: www2.SAS.com/proceedings/sugi30/213-30.pdf (last accessed 12 May 2009).
54. Blough DK, Ramsey SD. Using generalized linear models to assess medical care costs. *Health Serv Outcomes Res Methodol* 2000; 1: 185–202.
55. Beyersmann J, Wolkewitz M, Schumacher M. The impact of time-dependent bias in proportional hazards modeling. *Stat Med* 2008; 27: 6439–6454.
56. Centers for Disease Control and Prevention. Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1)—United States, May–August 2009. 2009. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm58e0929a1.htm (last accessed 16 September 2010).